Treatment of persistent gross hematuria with tranexamic acid in autosomal dominant polycystic kidney disease

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Abstract: BACKGROUND/AIMS: In this retrospective study we aimed to compare the effect of tranexamic acid (TXA) vs etamsylate, two hemostatic agents, on hematuria duration in autosomal dominant polycystic kidney disease (ADPKD) patients with persistent gross hematuria. METHODS: This is a retrospective study of 40 patients with ADPKD and macroscopic hematuria. 20 patients receiving TXA and snake venom blood clotting enzyme injection were compared with 20 matched patients receiving etamsylate and snake venom blood clotting enzyme injection. The primary outcome was hematuria duration and the secondary outcomes were blood transfusion requirements and adverse events. RESULTS: The hematuria duration was shorter in the TXA group compared with the etamsylate group (4[3-5] d vs 7[6-10] d, P<0.001). The volume of blood transfusion tended to be less in the TXA group than in the etamsylate group (300±115 ml vs 486±195 ml, P=0.12), and the number of patients needing a blood transfusion also tended to be lower [20% (4/20) vs 35% (7/20), P=0.29]. TXA and etamsylate were equally well tolerated and no serious adverse events were observed in both groups. CONCLUSIONS: Our study indicates that TXA treatment was more effective than etamsylate in stopping bleeding in ADPKD patients with persistent gross hematuria.

DOI: https://doi.org/10.1159/000474961

Kidney & Blood Pressure Research

Kidney Blood Press Res 2017;42:156-164
DOI: 10.1159/000474961
Published online: April 10, 2017
Accepted: January 17, 2017

Original Paper

Treatment of Persistent Gross Hematuria with Tranexamic Acid in Autosomal Dominant Polycystic Kidney Disease

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Key Words
Autosomal dominant polycystic kidney disease (ADPKD) • Persistent gross hematuria • Tranexamic acid (TXA) • Etamsylate • Hyperfibrinolysis

Abstract
Background/Aims: In this retrospective study we aimed to compare the effect of tranexamic acid (TXA) vs etamsylate, two hemostatic agents, on hematuria duration in autosomal dominant polycystic kidney disease (ADPKD) patients with persistent gross hematuria. ***Methods:*** This is a retrospective study of 40 patients with ADPKD and macroscopic hematuria. 20 patients receiving TXA and snake venom blood clotting enzyme injection were compared with 20 matched patients receiving etamsylate and snake venom blood clotting enzyme injection. The primary outcome was hematuria duration and the secondary outcomes were blood transfusion requirements and adverse events. ***Results:*** The hematuria duration was shorter in the TXA group compared with the etamsylate group (4[3-5] d vs 7[6-10] d, P<0.001). The volume of blood transfusion tended to be less in the TXA group than in the etamsylate group (300±115 ml vs 486±195 ml, P=0.12), and the number of patients needing a blood transfusion also tended to be lower [20% (4/20) vs 35% (7/20), P=0.29]. TXA and etamsylate were equally well tolerated and no serious adverse events were observed in both groups. ***Conclusions:*** Our study indicates that TXA treatment was more effective than etamsylate in stopping bleeding in ADPKD patients with persistent gross hematuria.

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease and it is characterized by the gradual expansion of countless renal cysts in bilateral kidneys leading to end stage renal disease (ESRD) [1]. The most common complications in ADPKD include hypertension, cyst hemorrhage, cyst infection, and renal calculi. In many parts of the world including China and the United States, ADPKD is still an untreatable kidney disorder, and only supportive therapies are available to control and reduce complications [2-4].

Cyst bleeding is a frequent and sometimes serious complication in ADPKD [5]. If a hemorrhagic cyst is connected to the kidney collecting system, patients may manifest with gross (macroscopic) hematuria. About 42% to more than 50% of ADPKD patients experience at least one episode of gross hematuria [6], and gross hematuria may be the initial diagnostic clue in up to 20% of ADPKD patients [6]. During an episode of gross hematuria, patients develop macroscopic hematuria and abdominal or loin pain. In most instances, gross hematuria is well controlled by conservative treatment such as strict bed rest, use of hemostatic agents and blood transfusions. In severe cases, i.e. when gross hematuria is prolonged for more than one week and still does not cease with conservative medical therapies, patients may need invasive treatment involving renal transcatheter arterial embolization (TAE), and in rare cases nephrectomy.

In the past, several approaches have been used to treat persistent gross hematuria in order to avoid prolonged hospitalization and invasive procedures [7-11]. Among these, tranexamic acid (TXA), a potent antifibrinolytic agent, is reported to be an effective drug to stop serious gross hematuria in ADPKD patients [9-11]. However, the evidence for efficacy of TXA treatment in ADPKD is limited since only 8 ADPKD patients were involved in a prospective uncontrolled study and two other TXA treated ADPKD patients were reported as case studies. Etamsylate is a widely-used hemostatic agent, which displays therapeutic benefits in dysfunctional uterine bleeding, periventricular hemorrhage, and surgical or postsurgical capillary bleeding through improving platelet adhesiveness and restoring capillary resistance [12]. We have used etamsylate as a hemostatic agent to stop cystic bleeding in clinical practice in our department. Snake venom blood clotting enzyme is a procoagulant and routinely used as a hemostatic agent in our clinics. It is derived from snake venom which contains a mixture of biologically active substances that interact with the hemostatic system [13].

In the present retrospective study, 40 ADPKD patients with a definite diagnosis of persistent gross hematuria were enrolled. Their clinical data were analyzed in order to compare the efficacy and safety of TXA vs etamsylate treatment for persistent gross hematuria in ADPKD.

Study Population and Methods

Participants

This retrospective chart review study was performed using the database of the Nephrology Department of Changzheng Hospital, the Second Military Medical University. We screened for ADPKD patients suffering from gross hematuria as initial symptom on admission and without any invasive intervention including TAE and nephrectomy from January 2010 to July 2015. A total of 370 ADPKD patients with gross hematuria were identified (Fig. 1).

Inclusion and exclusion criteria

Every patient had an established diagnosis of ADPKD as defined by the criteria of Pei *et al* [14]. Patients were selected for the study if they presented with gross hematuria as initial symptom, which lasted for more than one week and were unresponsive to conservative treatment including snake venom blood clotting

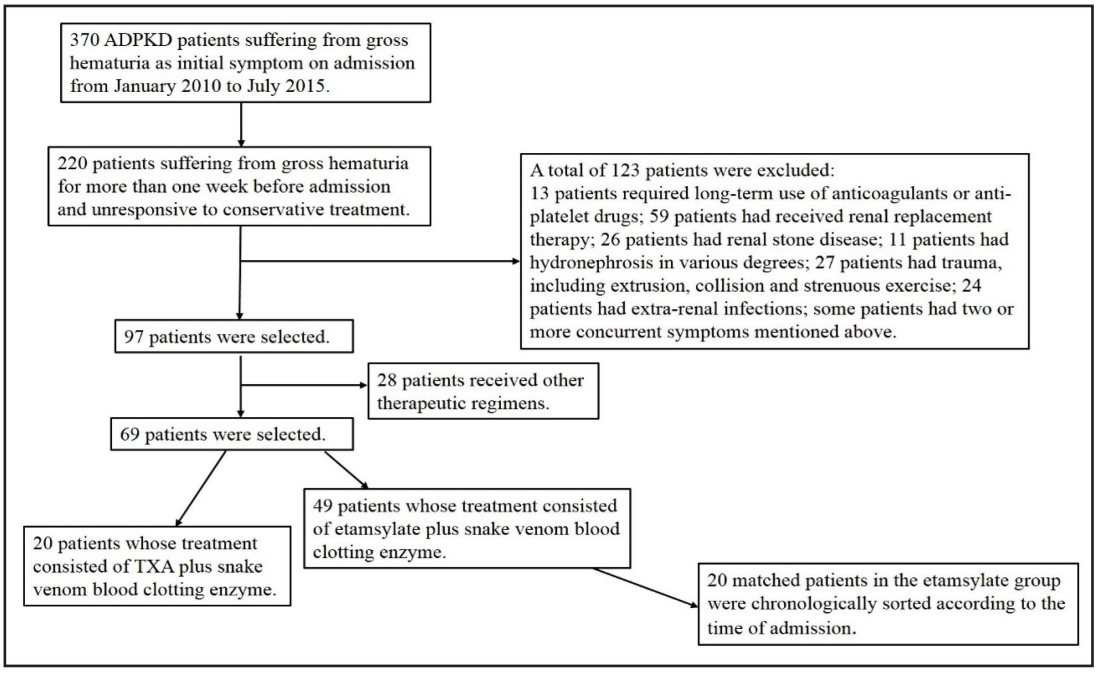

Fig. 1. Flowchart of TXA/etamsylate study in ADPKD patients.

enzyme. Among them, 220 patients had gross hematuria persisting over one week before admission and were unresponsive to conservative treatment (Fig. 1). Patients with the following conditions were excluded: requiring long-term use of anticoagulants or anti-platelet drugs due to various reasons, having received renal replacement therapy (dialysis or kidney transplantation), concurrent renal stone disease, tumors of the urinary system, hydronephrosis, trauma or extra-renal infections. Before or during hospitalization, patients routinely underwent renal magnetic resonance imaging (MRI) or MRI of urinary system (MRU) to rule out tumors of the urinary system or hydronephrosis. In accordance with inclusion criteria described above, 97 patients were selected for further analysis (Fig. 1). Among these 97 patients, 20 patients who were treated with the TXA [4-(aminomethyl) cyclohexanecarboxylic acid; Wuzhou pharmaceutical company, Guangxi, China] plus snake venom blood clotting enzyme (a mixture of batroxobin and phospholipids dependent coagulation factor X activators, Zhaoke pharmaceutical company, Hefei, China) were designated as the TXA group. The same number of matched patients whose treatment consisted of etamsylate (2,5-dihydroxy-benzene-sulfonate diethylammonium salt, Jiuzhou pharmaceutical company, Anyang, China) and snake venom blood clotting enzyme was chronologically sorted according to the time of admission and named as the etamsylate group. Patients in the etamsylate group were matched with patients in the TXA group with respect to age, sex, serum creatinine, and hemoglobin concentration on admission. This study was approved by the Ethics Committee of Changzheng Hospital.

Medical treatment during hospitalization

Patients in both groups were asked to observe strict bed rest. Erythropoietin (EPO) was used in patients with anemia. The dosage of EPO varied from 10,000 U to 18,000 U per week. Some patients received transfusion of red cell suspension. During bleeding, some patients had urinary tract infections as shown by fever development, abdominal or loin pain, or increase in white blood cell count in urine. Patients with concurrent urinary tract infections received antibiotic therapy according to the results of pathogen culture and sensitivity of the drugs. Combined administration of water soluble antibiotic and fat soluble antibiotic were used before the drug sensitivity test. Antibiotics taken in our study mainly included cephalosporins, metronidazole, and quinolones. Upon hospital admission, patients in the TXA group were given intravenous drip of TXA and at the same time also given snake venom blood coagulation enzyme by intramuscular injection (1000 U) once followed by intravenous injection (1000 U) once daily until the disappearance of

macroscopic hematuria for 48h. The dosage of TXA was adjusted according to serum creatinine levels in patients with impaired renal function: for patients with serum creatinine levels <250 μmol/L, 10 mg/kg intravenously (IV) injection twice daily; for patients with serum creatinine concentrations of 250 to 500 μmol/L, 10 mg/kg IV injection once daily; for patients with serum creatinine levels >500 μmol/L, 5mg/kg IV injection once daily [15]. Thus most patients in the TXA group were administrated with TXA at the dose of 0.5 g via IV injection once or twice daily. Only for patients whose serum creatinine levels >500 μmol/L, the dosage of 0.25 g IV injection once daily was given. Upon admission, patients in the etamsylate group were given an intravenous drip of etamsylate 1000 mg twice daily until the disappearance of macroscopic hematuria for 48h. The etamsylate group was also given snake venom blood coagulation enzyme at the same time by intramuscular injection (1000 U) once followed by intravenous injection (1000 U) once daily until the disappearance of macroscopic hematuria for 48h.

Outcomes

The primary outcome of our study was hematuria duration. Given that all patients enrolled had suffered from gross hematuria over 1 week before admission, hematuria duration was defined as the period from the day on admission to the day when macroscopic hematuria was disappeared. Patients whose microscopic hematuria were not stopped by the treatments and needed embolization or nephrectomy were defined as treatment failures, and excluded for hemostatic time calculation. The secondary outcomes included blood transfusion volume and rate, change in renal function, change in blood coagulation and fibrinolysis parameters, and adverse events, including treatment failures. We recorded demographics, duration of gross hematuria before admission to our department, ultrasound examination results and clinical biochemistry parameters before and after receiving medical treatment, such as hemoglobin, platelet count, urine red blood cell, fibrinolysis parameters (plasma fibrinogen degradation products [FDP], D-Dimer and fibrinogen [Fg]) and coagulation parameters (prothrombin time [PT], activated partial thromboplastin time [aPTT]), serum creatinine and estimated glomerular filtration rate (eGFR). The eGFR was calculated by the CKD-EPI formula. Once the macroscopic hematuria was stopped, aforementioned parameters were re-examined. In addition, adverse events due to drugs especially TXA were our important observational items.

Statistical Analysis

Continuous variables accorded with normal distribution were expressed as mean ± standard deviation, otherwise were expressed as median [interquartile range (IQR)]. Hematuria duration, which was skewed distributed, was presented as median [IQR]. Categorical variables are expressed as percentages. Clinical and laboratory parameters were compared using a two-sample t-test, Mann-Whitney U test or Chi-squared test, as appropriate. Changes during treatment within each group were analyzed with a paired t-test. All analyses were conducted using SPSS Version 21.0 statistical software. A P value < 0.05 was considered significant.

Results

General Characteristics of the Patients at Baseline

The baseline data of the two treatment groups are shown in Table 1. The treatment groups were well matched regarding age, sex, systolic and diastolic blood pressure, eGFR, and kidney length. Bleeding time before admission did not differ significantly between the two groups. Furthermore, the baseline coagulation and fibrinolysis parameters in both groups were also similar (Table 2).

The Primary Outcome of Treatment

The mean time to achieve hemostasis was significantly shorter in the TXA group compared with the etamsylate group, amounting to 4[3-5] days vs 7[6-10] days (P<0.001, Table 3 and Fig. 2).

The Secondary Outcomes of Treatment

The volume of blood transfusion in patients in the TXA group was numerically lower

Table 1. Baseline demographics and clinical characteristics of treatment groups

	TXA group	Etamsylate group	P value
Age(years)	49±9	52±9	0.39
Sex(male/female; number/number)	12/8	11/9	0.75
SBP(mmHg)	138±11	136±9	0.81
DBP(mmHg)	82±8	80±7	0.89
Bleeding time before admission (d)	10[7-10]	8[7-10]	0.59
Blood WBC (*10^9/L)	9.2±2.6	9.1±4.2	0.97
Blood CRP (mg/L)	63.0±43.0	61.1±42.4	0.89
Urine WBC (/μl)	185±169	144±217	0.51
Longitudinal diameter of left kidney (mm)	186±22	184±30	0.78
Longitudinal diameter of right kidney (mm)	175±20	174±29	0.94

Annotation 1 : SBP: systolic blood pressure; DBP: diastolic blood pressure; CRP: C- reactive protein; WBC: white blood cell; d: day. Longitudinal diameter of kidneys were measured by ultrasound examination; values for continuous variables are presented as mean ± standard deviation or median [interquartile range]. P <0.05 represents significance.

Table 2. Coagulation and fibrinolysis parameters within two groups during the treatments

▽

	TXA group		P1	Etamsylate group		P2	P3	P4
	before	after	value	before	after	value	value	value
PT (sec)	14.0±0.9	13.6±0.8	0.06	13.2±1.5	13.4±0.9	0.66	0.06	0.44
aPTT (sec)	41.4±3.8	37.8±4.5	0.35	40.3±5.2	38.2±3.5	0.78	0.62	0.67
Fg (g/L)	4.4±1.6	3.9±1.2	0.12	3.7±1.5	3.4±1.5	0.20	0.20	0.23
FDP (mg/L)	24.9±9.7	10.7±4.6	<0.001	24.2±7.9	23.8±7.8	0.78	0.79	<0.001
DD (μg/L)	9055.9±5220.9	2321.6±1597.2	<0.001	7766.0±5719.9	7611.5±4099.8	0.87	0.46	<0.001

Annotation 2: PT: prothrombin time; aPTT: activated partial thromboplastin time; Fg: fibrinogen; FDP: fibrinogen degradation products; DD: D-dimer; sec: second. Data are given as mean ± standard deviation. P1 and P2 represent intra-group comparisons before and after medical treatment, respectively; P3 and P4 represent inter-group comparisons before and after medical treatment respectively. P<0.05 represents significance.

Table 3. Clinical course and related parameters within two groups during the treatments

	TXA group		P1	Etamsylate group		P2	P3	P4
	before	after	value	before	after	value	value	value
Hemoglobin (g/L)	90±15	86±12	0.02	96±22	93±20	0.08	0.35	0.20
PLT (*10^9/L)	229±108	248±85	0.46	188±58	244±117	0.02	0.14	0.91
Scr (μmol/L)	260±219	258±215	0.97	271±245	267±249	0.96	0.83	0.89
eGFR (ml/min/per 1.73 m^2)	35±23	35±24	1.00	40±24	39±25	0.91	0.54	0.63
Urine RBC (/μl)	15371±17597	144±272	<0.01	15743±16759	1064±2156	<0.01	0.95	0.07
Hemostatic duration (d)	4[3-5]			7[6-10]				<0.001
Total Volume of blood transfusion (ml)	300±115			486±195				0.12
Blood transfusion rates	20%			35%				0.29

Annotation 3 : PLT: platelet; Scr: serum creatinine; eGFR: estimated glomerular filtration rate; RBC: red blood cell; d: day. Values for continuous variables are presented as mean ± standard deviation or median [interquartile range]; values for categorical variables are presented as percentages; P1 and P2 represent intra-group comparisons before and after medical treatment respectively; P3 and P4 represent inter-group comparisons before and after medical treatment respectively. P<0.05 represents significance.

compared with the etamsylate group (300±115 ml vs 486±195 ml, P=0.12, Table 3), and the number of patients needing blood transfusions in the TXA group tended to be less than that in the etamsylate group [20% (4/20) vs 35% (7/20), P=0.29, Table 3].

Table 4 shows the adverse events (AE) that occurred during hospitalization. In the etamsylate group, 1 patient needed nephrectomy of the affected kidney; 2 patients underwent segmental renal arterial embolization of the affected kidney. While in the TXA group, 1 patient underwent nephrectomy, and none underwent embolization of the affected kidney.

Thus, the treatment failures in the TXA group tended to be less than in the etamsylate group [5% (1/20) vs 15% (3/20), P=0.60]. A similar number of patients developed fever (13 vs 12) or were treated with antibiotics (17 vs 16) in the TXA vs etamsylate groups.

Additional AE: In the TXA group, two patients suffered from dysuria and achieved remission after urethral catheterization. No clot was found during urethral catheterization. Other patients did not have obstructive urinary symptoms. Besides, no other serious adverse events including deep vein thrombosis or neurological abnormalities were observed in both groups.

Table 4. Adverse events in two groups during the treatments

	TXA group (N or %)	Etamsylate group (N or %)	P value
Fever development	13	12	0.74
Application of antibiotics	17	16	1.00
Nephrectomy	1	1	1.00
TAE	0	2	0.47
Ratio of treatment failures	5%	15%	0.60
Dysuria	2	0	0.47
Other serious adverse events	0	0	

Annotation 4: TAE: renal transcatheter arterial embolization; N: number. The ratio of treatment failures were defined as number of patients unresponsive to the TXA or etamsylate treatment and needing embolization or nephrectomy to the total number patients in the group.

During hospitalization, renal function of patients in both groups remained stable (Table 3). The urine red blood cell counts were significantly decreased in both groups after medical treatments (Table 3). Levels of plasma fibrinogen degradation products (FDPs) and D-dimer were significantly decreased after treatment in the TXA group (Table 2). However, this was not observed in the etamsylate group (Table 2). In addition, levels of coagulation parameters (PT, aPTT) and fibrinogen were not significantly changed after the treatments in both groups (Table 2).

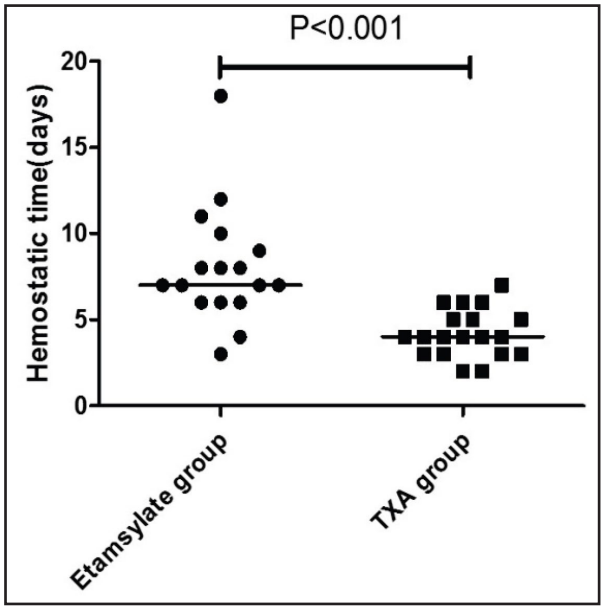

Fig. 2. Hemostatic time after the TXA or etamsylate treatments. Of a total of 40 ADPKD patients enrolled in this study, 17 patients in the etamsylate group and 19 patients in the TXA group were analyzed for hemostatic time. And other 4 patients who received embolization or nephrectomy were excluded for hemostatic time calculation. The median value of hemostatic time was shown as a horizontal line.

Discussion

Excessive angiogenesis [16-18] and secondary hyperfibrinolysis [19] especially local hyperfibrinolysis [7] may account for the development of persistent gross hematuria in ADPKD patients. Antifibrinolytic agents are used to treat ADPKD patients with persistent gross hematuria [7-11]. Among them, TXA is a potent antifibrinolytic agent, which exerts antifibrinolytic effect through reversibly blocking the binding of plasminogen to fibrin [20].

In the present retrospective study, 40 ADPKD patients with persistent gross hematuria receiving TXA or etamsylate treatment were studied retrospectively. We found that TXA halted the bleeding more effectively than etamsylate in ADPKD patients. First, the bleeding duration of the TXA group was significantly shorter than that of the etamsylate group.

Second, the volume of blood transfusion in the TXA group appeared to be reduced compared with that in the etamsylate group, and the blood transfusion rate in the TXA group tended to be lower than that in the etamsylate group, which is consistent with previous reports that use of TXA could reduce blood loss and blood transfusion rate in major surgeries [21-25]. Third, the number of nephrectomies or embolizations was lower in the TXA group.

The reason why TXA was more effective than etamsylate to stop persistent gross hematuria might be due to the excessive hyperfibrinolysis existing locally in polycystic kidneys [7]. In this study we found that the plasma D-dimer and FDPs, two systemic fibrinolysis parameters, were significantly decreased in patients of the TXA group, confirming that TXA inhibited the hyperfibrinolysis in polycystic kidneys. In our previous report, we observed a significantly lower thrombocyte count in ADPKD patients with lower eGFR and higher TKV, implying that advanced ADPKD patients are at high risk for cystic bleeding [26]. Thus the increase of thrombocyte number and/or enhancing thrombocyte activity could be important to control cystic bleeding in advanced ADPKD patients. In the current study, the platelet count was increased by etamsylate treatment. Besides, etamsylate is a hemostatic agent working through improving platelet adhesiveness and restoring capillary resistance [12]. However, the less potent effect of etamsylate on persistent gross hematuria in ADPKD was probably due to the reported mild hemostatic effect of this agent and less pathogenic importance of platelets in ADPKD.

Intravenous TXA is eliminated entirely through the kidneys and could accumulate in patients with chronic renal failure (CRF) [15]. Adverse effects of TXA treatment have been reported in kidney diseases [27-29]. Koo et al. reported a case of acute renal cortical necrosis induced by large dosage of TXA [29]. The dosage of TXA we used in this study was taken according to suggestions recommended by Andersson et al. for TXA treatment in CRF [15]. Indeed, no renal damage was observed during the TXA treatment in our study, and levels of serum creatinine and eGFR remained relative stable. Among several patients, anemia improved and serum creatinine were even moderately decreased after correction of prerenal hypovolemia. TXA treatment may induce thromboembolic complication and urinary obstruction by clots [30-33]. Hydration and alkalinizing urine therapy can be used to prevent urinary obstruction. We found that only two patients in the TXA group suffered from dysuria and achieved remission after undergoing urethral catheterization. No clot was found during catheterization in this study. In addition, in the TXA group, PT and aPTT were not obvious changed during the treatments suggesting that TXA had no powerful impact on coagulation. Overall, TXA was well tolerated and serious or severe adverse events were rare [34]. The adverse effects of TXA are dose dependent, thus taking the lower effective dosage of TXA could prevent severe adverse events. Therefore, we adjusted the dosage of TXA according to renal function in ADPKD patients in order to achieve the safety.

In our study, there were 1 patient from the TXA group and 3 patients from the etamsylate group whose gross hematuria did not achieve remission and received nephrectomy or TAE. Kidney volumes of these patients were rather large and the ultrasonic test showed that the longitudinal diameter of these kidneys were all above 240 millimeter. Furthermore, every one of them underwent cystoscopy for several times and showed hemorrhage from the same side every time. The reason why one patient in the TXA group responded poorly to TXA may be explained by the extensive angiogenesis and secondary hyperfibrolysis in large kidneys.

Conclusion

ADPKD patients, who suffer from cyst hemorrhage which is resistant to conservative treatment and hemostatic drugs, TXA with adjusted dosage can achieve hemostasis more effectively than etamsylate. This may result in a lower requirement of blood transfusions and less invasive procedures, protection of renal function and improvement in the quality of life of ADPKD patients.

There are several limitations in our study: 1) a retrospective study; 2) the small sample size; 3) lack of information on longtime follow up. A multicenter randomized controlled trial (RCT) should now be performed to better clarify the effectiveness and safety of TXA treatment in ADPKD patients with persistent gross hematuria.

Disclosure Statement

The authors state that they have no conflict of interest.

Acknowledgements

This work was supported by Support from Shanghai Natural Science Foundation NO.16ZR1436700 to YM, The National Natural Science Foundation of China (NSFC) NO.81400687 to DC, Shanghai International Science and Technology Cooperation Fund Project (0954070200) to CM, National Science & Technology Pillar Program (ID: 2013BAI09B04) and National Natural Science Foundation of China General Projects (31371172), Systemic Redesign and Demonstration for Early Detection, Evaluation and Management of Chronic Kidney Disease in Shanghai (SCREENING Study GWIV-18).

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